DRAFT 1

"RESPIRATORY HEALTH EFFECTS OF PASSIVE SMOKING: LUNG CANCER AND OTHER DISORDERS"

A commentary on issues relating to lung cancer in the May 1992 SAB Review Draft

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Date : June 1992

Signed :

Date .

*Any views expressed are those of the author and not of any other person or company

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1. My background and qualifications

I am an M A of Oxford University, having read mathematics with postgraduate statistics. I am a Fellow of the Royal Statistical Society and an Honorary Research Fellow of the Institute of Cancer Research, Division of Epidemiology. I was employed as statistician and later as research co-ordinator to the Tobacco Research Council from 1966 to 1979. Since 1979, I have been an independent consultant in statistics and adviser in epidemiology and toxicology to a number of tobacco, pharmaceutical, chemical, and other companies. Since 1984, I have been director of P.N. Lee Statistics and Computing Ltd. I have had some 100 papers published, have contributed to two IARC monographs on analysis of animal experiment data, and have served as editor of standard reference books on smoking habits. I have been heavily involved in work on the possible health effects of environmental tobacco smoke over the last 10 years or more and have written two books on the issue, as well as over 10 papers and many letters on the subject. The EPA report itself makes numerous references to my work, including noting that I was the first to bring to attention the potential for bias due to misreported smoking habits - an issue that is given considerable attention in the report.

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2. Introduction

In September 1990 I submitted detailed comments on the earlier, 1990, Review Draft of this report. As annexes to these comments I attached text and tables of "a detailed review of epidemiological evidence relating ETS to the risk of cancer, heart disease and other causes of death in adults who have never smoked", cited as a reference on page R-29 of the 1992 Review Draft. This has subsequently been published as a book, "Environmental Tobacco Smoke and Mortality", by Karger, Basle (1992), copies of which have been made available to EPA and the Scientific Advisory Board (SAB). In a number of places I refer to my book as justification for points I make, referring to it as "my ETS book". The Review Draft commented on here is, for convenience, referred to as "EPA2" to distinguish it from the earlier draft.

In November 1991 I prepared a note, "Correcting meta-analyses of the association of lung cancer in females with spouse (or household) exposure for bias due to misclassification of active smoking status", which was also submitted to the EPA.

This document provides further comments on EPA2. Although it is in many ways a substantial improvement on the earlier draft (EPA1), and some points I made have been taken into account (my contribution having been acknowledged on page xvii), there remain a considerable number of weaknesses in it which justify further detailed reconsideration of it.

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3. Hazard identification II: Interpretation of Epidemiologic Studies on ETS and Lung Cancer (Chapter 5) and Population Risk of Lung Cancer from Passive Smoking (Chapter 6)

My comments relate mainly to these two chapters of EPA2 and to the Appendices which relate to them. Some other comments on EPA2 are presented in section 4.

It is convenient, first, to describe briefly the various steps EPA2 goes through to reach its conclusion that "ETS is a Group A human carcinogen" and that "an estimated range of 2,500 to 3,000 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States". The main steps can be summarized as follows:

1) Select the epidemiological studies to be given detailed attention.
2) Select the index of ETS exposure (spouse smoking or nearest equivalent), and sex (females) to be studied.
3) Choose the relative risk estimate most appropriate to each study.
4) Adjust relative risk estimates on a study by study basis downward to account for smoking habit misclassification using methodology developed by Wells.
5) Use fixed effects meta-analysis, with 90% confidence intervals, to demonstrate the existence of a significant association between lung cancer and spousal smoking in Greece, Hong Kong, Japan and USA, but not in Western Europe or China.
6) Use trend tests to study the dose-response relationship.

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7) Consider and reject confounding by other risk factors as a source of systematic bias in the studies.

8) Consider specific study weaknesses, and conclude that "there are no additional sources of bias . . . that would systematically cause higher observed relative risk estimates" and that "the observed association between ETS and lung cancer cannot be explained by bias".

9) Reject the cigarette-equivalents approach for estimating population risk.

10) Restrict attention to the US epidemiological studies for the purpose of estimating population risk.

11) Adjust upward meta-analysis estimates of lung cancer risk associated with spousal smoking and take into account ETS exposure from sources other than the spouse ("background ETS") by a cotinine based Z-factor.

12) Use these risk estimates, compiled with independent estimates of relative risk for ever/never smokers and of population and total numbers of lung cancer deaths, to estimate mortality rates and numbers of lung cancer deaths associated with ETS among never smokers. By this method 1500 deaths per year, 470 from spousal ETS and 1030 from background ETS, are attributed to ETS exposure in never smoking women.

13) Assume mortality rates among never smoking men are increased to the same extent by ETS as they are in women and thus estimate 500 deaths per year, 80 from spousal ETS and 420 from background ETS, are attributed to ETS exposure in never smoking men.

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14) Assume mortality rates among former smokers who have quit for at least five years are increased to the same extent as before, and thus estimate a further 1060 deaths per year are attributed to ETS, 440 in women and 630 in men (sic).

15) Recalculate deaths attributable to ETS based on relative risks and Z-factor estimates from the Fontham study, yielding a total of 2,500 to 3,300 deaths per year as against 3,060 deaths per year based on the 11 US studies.

In the sections that follow I comment on these steps in essentially this order.

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3.1 Selection of epidemiological studies

My ETS book presented a detailed analysis of data from 28 studies which provided data for women, whereas EPA2 considers data from 30 (a 31st, KATA, being referred to in Table 5-1 but not actually producing any relevant data). They include three studies I did not. Two were very recent studies, FONT and LIU, only referred to as a "note added in proof" by me. The BUTL (Coh) study was only available as a dissertation, which I did not have, it being clear it was based on very few lung cancer deaths among never smokers. There is every reason for EPA2 to include these studies, but no valid reason I can see to omit the second case-control study by Kabat and Wynder which I included, which was reported in moderate detail at the 1990 Washington meeting of the Toxicology Forum, the proceedings of which are publicly available. Given the principal author is an SAB member, one would have thought it easy enough for EPA to get fuller details if they required them. It should be noted that it is a US study which produces a relative risk (RR) estimate less than 1, 0.90 (95% CI 0.46-1.76), which will slightly reduce meta-analysis estimates.

3.2 Restrict attention to females

It is clear that the data for females are based on far more deaths among never smokers and are presented in much more detail in the source papers than are the data for males. It is also clear (both from pp 146-150 of my ETS book and from pp 6-16 and 6-17 of EPA2) that the relative risk associated with spousal exposure in US males can readily be explained by a very modest amount of smoking

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habit misclassification (somewhat less than implied by results from community based surveys), implying there is no actual evidence from the data in males of an underlying true association of lung cancer with spousal exposure. In these circumstances there are two main alternatives:

(i) Use the data for males, both as a partial counterweight to the evidence in females in evaluating whether ETS causes lung cancer, and directly in the estimation of deaths due to ETS in nonsmokers.

(ii) Ignore the male data and use female-based ETS risk estimates to estimate risk in males.

EPA2 has used the latter approach, and has even argued that this may underestimate deaths since males are probably exposed to more background ETS exposure than females. Although some 1000 of the total of 3000 animal lung cancer deaths they attribute to ETS are in males, they only attribute a range as narrow as 800 to their overall estimate (of 2500 to 3300 deaths). In other words they totally ignore what the actual male data are telling them, that there may in fact be no deaths attributable to ETS in males. In my view this is the wrong approach. EPA should have been totally "up front" giving the male data alongside the female data, and showing under varying degrees of assumed misclassification what the corrected relative risk would have been, and taking full account of the uncertainty resulting from this in their final estimates.

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3.3 Restrict attention to spousal smoking data

As is made abundantly clear in my ETS book, although the crude data show an association of spousal smoking with lung cancer risk, they show no association whatsoever with indices of ETS exposure at work or in childhood. Based on 13 independent relative risk estimates for workplace exposure and 11 for childhood exposure I estimated (on pp 117-9) a meta-analysis of 0.98 (95% limits 0.89-1.08) for workplace and 0.98 (95% limits 0.86-1.12) for childhood exposure. EPA2 does not even make it clear such data exist, let alone that they show no association. There is no discussion at all in the report as to why attention should be concentrated on spousal exposure. Clearly, concentrating on the index that does show an association at the expense of two other indices that do not must bias interpretation of the overall evidence, regardless of whether the data for the first index are somewhat more abundant than for the other two. In my view the workplace and childhood data are crucial to understanding the whole evidence and must not be ignored. It is ludicrous, in particular, to attempt to estimate effects of non-spousal exposure to ETS indirectly (from evidence from spousal exposure coupled with evidence from relative cotinine values in women married and not married to a smoker), and to ignore totally direct evidence that actually is available on other sources of ETS exposure. In 1986, when nearly all the published data related only to spouse smoking as an index, it was acceptable, as the NRC and USSG did, to concentrate only on this. Now, this is manifestly not the case and it is a very serious weakness of EPA2 that it does so.

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3.4 Have the most appropriate relative risk estimates been used?

Section 5.2.1 of EPA2 is intended to explain the criteria and to select one spouse smoking relative risk estimate from another, but in fact it is rather unclear. Because "spouse ever smoked" is the most common index of ETS exposure one would have thought it logical, to minimize between-study heterogeneity, to choose an index as close to this as possible where a choice is available, but it is not clear that any such decision rule was used. I went through the Tables in EPA2 and compared them with Table 13.4F of my ETS book. A number of minor differences were noted, but I will limit attention here to the larger differences where it seems that EPA have used an inappropriate RR value in their meta-analyses.

GARY - Why did EPA use 1.31 for the crude estimate, based on "husband's smoking habits at home" when the alternative of 1.23 based on "husband's total smoking habits" given in Table 5 of the source reference is clearly more appropriate for comparability with other studies?

JANE - Why did EPA use 0.86 for the crude estimate, based on ETS exposure in adulthood rather that estimate, as I did, a weighted average of the estimates of 0.93 and 0.44 for direct and surrogate interviews? As described on p 102 of my ETS book I obtained an RR of 0.75 with 95% limits of 0.47-1.20 for females.

LAMW - I would have thought it better to use the RR value of 2.01 for adenocarcinoma/spouse, than to extend the exposure criterion unnecessarily to include sources other than the spouse.

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SOBU - Again I would have thought it better to use the data for spouse exposure than to include other sources of exposure unnecessarily. 1.13 is a more appropriate estimate.

Had more appropriate estimates been used for GARF and JANE, and had the second Kabat study been included I have calculated approximately that the US meta-analysis relative risk would reduce by about 1.03 or 1.04 and move the lower 95% confidence limit very close to unity.

3.5 Has adjustment for misclassification been properly conducted?

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3.6 Is use of 90% confidence intervals appropriate?

Use of 90% confidence intervals corresponds to using one-sided tests of a hypothesis. They are in my view only appropriate where it can be ruled out a priori that if there is an effect of ETS it can only possibly be in one direction. In practice this is rarely the situation, and although some will argue it is the situation here, I doubt if our knowledge of low-dose carcinogenesis is adequate enough to be sure. In any case with various potential biasing factors about, relative risks significantly below unity may actually occur. I would prefer the use of 95% confidence intervals for comparability

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with generally accepted practice. 95% intervals were used by the NRC and USSC in their reports, for example. Switching from 95% intervals in EPA1 to 90% intervals in EPA2 comes over too much to me as if the authors were doing everything in their power to have the US meta-analysis RR come out as statistically significant, and I do not think regulatory authorities should come over in this way.

One minor point is that in some tables mixtures of 90% and 95% intervals are used. This is just confusing. Since it is absolutely trivial to convert one to the other there is just no reason to do this.

3.7 Is fixed-effects meta-analysis appropriate?

In Table 5-8 the results of studies are combined over country or continent by what is sometimes termed fixed-effects meta-analysis, which involves calculating a weighted mean, using as weights the inverse of the variance of each odds ratio. Such a procedure takes into account only within-study variation. As noted on page 5-10 of EPA1 there is an implicit assumption of homogeneity of relative risk within the studies being combined. But it is abundantly clear, from a simple examination of Table 5-8, that this condition is not held. The results for Hong Kong and for China are certainly statistically heterogeneous and taken as a whole the data show significant heterogeneity. In these circumstances it is usual (see e.g. Fleiss and Gross (1991) and de Simonian and Laird (1986)) to allow in the calculations for the possibility of between-study variation being greater than expected, using a random effects

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analysis. This results in an increase in the size of the confidence intervals of the combined estimates. At the very least, EPA should give a detailed discussion justifying why they failed to take into account any element of the significant between-study variation.

3.8 Should WUWI and LIU be considered separately?

EPA2, on page 5-10, argues that the two Chinese studies of WUWI and LIU are less likely to detect any true passive smoking effect because of the presence of indoor smoke from cooking and heating (in the case of the LIU study with smokey coal, known to cause lung cancer). Implicit in their argument is the belief that ETS and indoor smoke are not independent risk factors which act multiplicatively (otherwise there would be no special problem in detecting a potential ETS effect) but are factors which act in a similar manner, so that their effects are additive. In this situation it is true that the relative risk in relation to ETS exposure would be expected to diminish with increasing exposure of the population to indoor smoke. But it is also true that if this is the situation, an underlying assumption in standard meta-analysis, namely that the agent multiplies risk by a constant factor, then breaks down. To produce combined estimates would require either adjustment study-by-study for level of exposure of the population to indoor smoke from other sources or perhaps combining differences rather than ratios of risks. It is still possible to produce tests of the null hypothesis but rather more difficult to produce valid combined estimates. I am somewhat surprised that EPA do not appear

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to have thought of this problem at all, or are they assuming that in all populations except WUWI and LIU indoor smoke is negligible? Is this justifiable?

One point that is not discussed is why the covariate adjusted relative risk in the WUWI study should be significantly below 1. The explanation put forward by EPA would only explain why the relative risk should be not different from 1.

3.9 Use of trend tests

Section 5.3.2.3. of EPA2 is inadequate in a number of ways:

(i) It does not mention the fact that many of the sources of bias discussed, such as misclassification and confounding, would be expected not only to result in an artefactual association but also in an artefactual trend. For example, Lee (1987) demonstrated a clear tendency for heavier smokers to be more likely to marry smokers than are light smokers.

(ii) It does not make it clear that the test for trend to some extent duplicates the test for an association comparing the overall ETS exposed and non-exposed groups In LAMT, to cite only one example, the trend is significant despite the risk in the three exposed groups being very similar. An independent test would be to consider whether, within the exposed groups, risk rises with increasing dose. Layard (1990) calculated that none of the studies published up to that time has individually shown a statistically significant trend when

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calculated in this way. Overall, however, there is some tendency for risk to be higher in the highest exposure group than in the lower exposure group.

(iii) It is falsely stated that "dividing the data into small exposure categories" (as in a trend test) "decreases the power to detect a real effect". If there is an association between lung cancer risk and extent of ETS exposure, and if the exposure index is correlated with actual exposure, the trend test is much more powerful, not less. This argument that the results of the trend test are "especially compelling" is therefore false.

3.10 Confounding by other risk factors as a source of systematic bias

I find section 5.4.2. , on potential confounders, to be one of the weakest parts of the whole of EPA2. There are two major reasons for this. The first is that the apparent objectives are wrong. As judged by the second paragraph of 5.4.2.6., a confounding variable is seemingly required to explain fully the significant association of ETS exposure with lung cancer in Greece, Hong Kong, Japan and the United States, before it is considered relevant. Why should it not be part of the story only, with other confounders and other sources of bias also relevant? The second is that, for no good reason whatsoever, the document limits attention only to evidence from the epidemiological studies of ETS and lung cancer. There is a massive literature showing that various occupations increase risk of lung cancer (many are cited as definite causes by IARC and other authorities) but this is not referred to at all. There is also a

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massive literature on diet as a protective dietary factor and lung cancer and Section 5.4.2.6. scarcely echoes the conclusion of a recent review by Fontham (1990) that "The dietary studies have been notably consistent, finding an approximate 50% reduction in risk associated with high compared to low consumption of carotene-containing fruits and vegetables". This is despite the obvious difficulty in getting good dietary data which would tend to underestimate the true effect of diet. There is also good evidence that family history of lung cancer is an independent risk factor for lung cancer. (I am currently finalizing a review paper which concludes that the data show an approximate doubling of risk, that does not seem explicable in terms of confounding by age, smoking, family size, or other variables, and has been seen in studies where recall bias can probably be ruled out as an explanation). The impression given by EPA2, therefore, that these are not true lung cancer risk factors at all is most misleading.

In my ETS book, I presented on pp 133-142, detailed arguments why I believed confounding by diet and perhaps by other factors was relevant. I recommended that more work is needed to clarify the role of confounding more precisely. Though much work still remains to e done, I present in Annex B an interim analysis of data from a representative population of 9,000 men and women in the UK. From this analysis four general conclusions were reached:

1) Current smokers differ significantly from never smokers* in exposure to a variety of independent risk factors.

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2) The difference is virtually always in the direction of predicting an increased risk of disease in smokers independent of their smoking.

3) Where such a difference is seen, a difference in the same direction is nearly always seen in relationship to passive smoke exposure*.

4) For many risk factors, the magnitude of the difference in exposure in relation to passive smoking is sufficient to cause bias large enough to be important, when compared with the magnitude of the relative risk associated with passive smoking for diseases such as lung cancer.

(*In this analysis those who had not smoked were classified as passive or never smokers according to whether or not they lived with a smoker.)

It is absolutely evident that the conclusion of EPA2 that confounding by other risk factors can be ignored is erroneous.

The study of FONT is considered of high quality by EPA, and large enough to justify conducting population estimates of risk based on it alone. This study contains detailed data on diet, occupation, personal medical history, and other exposures of interest, but these data were not considered as potential confounding variables in the paper which appeared late in 1991. It would seem to me a relatively quick and easy task to organize a detailed analysis to be done looking at the effect of adjustment for

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these variables on the ETS/lung cancer relative risk estimate, and that EPA should organize this. (N.B. Care should be taken to take into account the well known fact that adjustment for inaccurately measured variables only partially corrects for the true confounding effect.)

3.11 Specific study weaknesses

Section 5.4.3. considers a range of possible study limitations and sources of uncertainty that might have caused bias in the epidemiological studies. For each potential biasing factor studies are categorized, in Table 5-14, as having or not having the factor, and there is discussion in general terms about whether particular factors are likely to cause upward bias, downward bias or bias in either direction. At the end of this discussion it is concluded that none of these additional sources of bias "would syatematically cause higher observed relative risk estimates". This is a remarkable and totally unjustified conclusion, for two reasons. Firstly, even non-systematic sources of bias, present to a great extent in a small number of studies, can materially affect the overall relative risk estimate. Secondly, and more importantly, EPA2 makes no attempt whatsoever to test, for any potential source of bias, whether the observed relative risk actually tends to differ in those studies classified by them as having it (a cross in Table 5-14A) and those not having it!

In my ETS book I did in fact carry out my own analyses along these lines. Following Breslow and Day (see quotation on pp 5-17 and

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18 of EPA2). I felt that the most serious potential sources of bias were those where there was a systematic difference between cases and controls in the circumstances in which the data were collected. As described in section 3.4.6 of my ETS book, I identified ten studies where the general principle of comparing "like with like" had clearly not been adhered to. The median relative risk in these studies (1.74) was substantially higher than in the other studies with no obvious weaknesses in this respect (1.17). This analysis suggests the EPA have underestimated the possibility that weaknesses specific to individual studies may have biassed the overall relative risk estimate.

The individual studies are reviewed in Appendix A of EPA2 with a briefer review given in section 3.4.4., which concentrates on potential biassing factors and on attributing a "tier" (study quality) number to each study. A weakness of the report is that no

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indication is given as to how the tier number was assigned. Was it purely subjective or to some extent semi-quantitative (i.e. assigning plus points for good features and minus points for bad ones)?

The interested reader may compare chapter 2 of my ETS book, which reviews each study individually, with Appendix A of EPA2. Annex G of this document summarizes some particular differences I noted on comparing the two sources. From this comparison I concluded

Probably will not use this

TO FOLLOW

3.12 Publication bias

In any review or meta-analysis of data from multiple studies it is absolutely standard to consider formally the possibility that publication bias might have occurred. In my ETS book (p 166) I concluded that some publication bias has occurred, though it appears it can explain only a part of the observed association. This was based on an analysis which demonstrated that the 8 studies (out of 28) showing the highest relative risk estimates were based on significantly ($p<0.05$) lower numbers of lung cancers than those 8 studies showing the lowest estimates. This was consistent with failure to publish results of small studies showing no association. Clearly publication bias is an issue EPA2 should have addressed.

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3.13 Failure to consider histological type

EPA2 does not compare and contrast results for different histological types of lung cancer. There is abundant evidence that smoking is much more strongly associated with risk of squamous and small cell cancer than with risk of adenocarcinoma, and if ETS is seen, crudely, as a smaller dose of active smoking (which EPA implicitly assume), it would be expected, if it had any effect at all, to be more strongly associated with risk of squamous and small cell cancer. As discussed in my ETS book (pp 109-111) the data here are in fact conflicting. Though some studies (GARF, PERS, TRIC) produce data seemingly consistent that the relationship is with squamous cell carcinoma, other studies (FONT, LAMT, LAMW and perhaps BROW) seem more consistent with an association with adenocarcinoma, and others who studied data by histological type (KOO, LEE, JANE, KALA) found a similar association, or lack of association, for squamous cell carcinoma as for adenocarcinoma.

The failure to find evidence of a stronger association of ETS with squamous cell carcinoma than with adenocarcinoma is clearly relevant and should certainly have been discussed.

3.14 The cigarette-equivalent approach

Section 6.3.1 notes that the report uses "the epidemiologic approach because of the abundance of human data from actual environmental exposures" stating that "the assumptions are fewer and more valid than for the cigarette-equivalents approach". However,

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the EPA do not list the assumptions behind the two approaches to allow a ready check of this statement. In my view, both approaches involve a very considerable number of assumptions and uncertainties indeed, and it would be preferable to present estimates by the EPA calculated using both approaches. This would give better insight into how contingent the estimates are on the approach used.

In fact, though there are obviously differences depending on the details of each approach, it is generally true that the cigarette-equivalents approach tends to produce much lower estimates, often by two or three orders of magnitude, than does the epidemiologic approach. While, in sections 6.2.1 and 6.2.2, results of other published risk assessments using both approaches are described, there are no summary paragraphs or tables to make it clear to the reader that the cigarette-equivalents approach does tend to produce much lower estimates. Furthermore, nowhere in the report is it made clear that the amount of particulate matter estimated to be retained in the lung by an average ETS exposed individual is as low as 0.05% of that retained by an average smoker, nor that the cotinine based estimate of relative nicotine uptake which is given as 1% (though my review of the evidence suggested 0.5%) is likely to mislead as nicotine in ETS may be absorbed without reaching the lungs. Nor is it made clear that in contrast (see my ETS book pp 123 and 124) the overall epidemiological evidence, if unbiassed, suggests that ETS exposure (from marriage to a smoker) is something like 10-20% of that from active smoking.

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The sharp conflict between the risks indicated by the cigarette-equivalents approach and those indicated by the epidemiologic approach is of great importance in evaluating the overall evidence. Not even to make it apparent to the reader that there is such a conflict, and to argue, as EPA do, that only the epidemiologic data should be used, biases the whole report.

3.15 Restriction to US studies

Now that there are data from a relatively large number of US studies I would agree that it is appropriate to restrict attention to US data only, when deriving estimates of risk applicable to the US. In any case, I believe that lack of good data on misclassification in Japanese and other Asian populations, would render if virtually impossible to use epidemiologic data from studies in this continent when deriving such estimates.

3.16 Adjustment for background ETS exposure

Three aspects of this adjustment procedure particularly concern me. The first is the possibility that misclassified smokers may severely affect the estimated Z value. As smokers typically have cotinine values that are more than 100 fold higher than that in nonsmokers, inclusion of only a small proportion of true smokers among self-reported nonsmokers may dramatically increase the mean cotinine and bias estimates of Z. There are two methods of getting round this problem. One is to delete subjects with a cotinine above a given value (perhaps 10% of average smokers levels) from the

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calculations. The other is to use medians, which are far less affected by a few aberrant values. I prefer using medians anyway, as the distribution of cotinine values is skew, but in any case one must not, as EPA2 have done, accept mean values where the misclassified smokers have not been deleted.

My second concern lies in the fact that the cotinine data from which the two values derive come from younger populations than are relevant for the older subjects in the epidemiological studies. It is apparent that as people get older, and particularly as they retire, they spend more time at home. The Z values derived from the population studies may therefore be marked underestimates, so that the numbers of deaths due to ETS are markedly overestimated.

My third concern is that the relative risk estimates used in some of the US studies (BUTL 2.01, CORR 1.90, HUMB 1.98) exceed 1.75, and are thus inconsistent with the Z value used to adjust for background. Equation 6-2, on page 6-11, of EPA2 would actually produce negative estimates of risk if this formula were applied to results for a single study. In theory, just as for misclassification status, adjustment should be study by study but this would not produce valid answers in this case, and it would not do so also if the relative risk were slightly less than Z. (A relative risk of 1.74 when adjusted for background would become over 100!) All this suggests to me that an appropriate adjustment procedure should take into account the variability of both the Z and the relative risk

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estimate, though at the time of writing I am not in a position to recommend what the procedure should be. In any event, at least some reference to the problem should be made.

3.17 Estimation of US female never smoking mortality rates by exposure to ETS

The formulae to derive mortality rates attributable to non tobacco smoke related causes, ever smoking, spousal ETS, and background ETS seem straightforward enough given assumed values of the number in the population, the number of lung cancers, the proportion of ever smokers, the proportion of never smokers exposed to spouse smoking, the relative risks associated with ever smoking and with spouse smoking, and the Z value.

Whether it is appropriate to use American Cancer Society data to estimate relative risks for ever smoking is, however, open to question. This population is of higher than average social status, being virtually all white, and being exposed less to occupational factors, so that their risk from non tobacco smoke related causes would be expected to be atypically low.

Another problem is that no account has been taken of misclassification in estimating ever smoker/never smoker relative risk. Elsewhere (Lee, 1991), I estimated, assuming 1% of ever smokers deny smoking on interview, that it would have the effect of reducing an earlier estimate of deaths attributable to ETS (by Wells) by a factor of as much as 20%.

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It is well known that there is substantial misdiagnosis of lung cancer on death certificates. It would be more appropriate to refer to "reported lung cancer deaths" than to "lung cancer deaths" when presenting results.

3.18 Extension of estimates for females to estimates for males

This has already been discussed in section 3.2. As noted there, the decision to ignore data for males, which show no association after adjustment for minimal misclassification, and to use female-derived relative risks to estimate risks for males is questionable. Certainly estimates of risk for males derived in this way are subject to extreme uncertainty that is not reflected properly in EPA2.

3.19 Extension of estimates for never smokers to ex-smokers

There is little or no direct epidemiological evidence on risk in relation to ETS exposure for ex-smokers (the study by Varela looked at this but found no effect) or on levels of ETS exposure in ex-smokers as distinct from never smokers. It is therefore impossible to make any reliable estimate based directly on relevant data. However to assume, as EPA have done, that risk estimates based on results for never smokers are applicable also to ex-smokers who have given up for five years or more seems remarkably simplistic. Might not effects of ex-smoking interact with those of ETS (if any)? Might not the situation depend on how long ago the smoker gave up, or why? There seems no scientific justification whatsoever for

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extrapolating estimates to ex-smokers. If EPA feel that they must say something about deaths in ex-smokers (and males) they should phrase their conclusions along the following lines: "Based on epidemiologic data for never smoking females we estimate a total of x_1 deaths (range y_1-z_1) to be attributable to ETS. Adequate data are not available to evaluate risk in never smoking males or in ex-smokers who have given up for five years or more, but if one assumes ETS increases risk to the same extent as for never smoking females it is estimated that a further x_2 deaths (range y_2-z_2) would be attributable to ETS".

3.20 Use of FONT to derive alternative estimates

It is certainly reasonable for EPA to have presented estimates based solely on FONT since it is large, and unusually has cotinine data to allow an internal estimate of the Z-value. However, it should be realized that, despite its Tier 1 classification, FONT does have some weaknesses:

(i) It is still ongoing and data are incomplete.

(ii) Although extensive data have been collected for dietary and other risk factors no attempt was made to adjust for them in analysis.

(iii) Response rates varied markedly between cases (84%) and controls (72%).

(iv) All population controls were self-respondents whereas next-of-kin responded for 34% of cases.

(v) Analyses presented failed to take into account what might be termed "relevant denominators". Thus the analysis of spousal

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ETS exposure is not limited to married women, the analysis of ETS from other household members is not adjusted for number of other household members, the analysis of occupational ETS exposure is not limited to working women, etc.

Also the results were somewhat unexpected in that they showed a significant association between spousal exposure and adenocarcinoma, only weakly related to active smoking, and showed no association between spousal exposure and squamous cell carcinoma, strongly associated with active smoking.

EPA2 does not make it clear whether the 2 values derived from the cotinine data in the controls were based on all the subjects, or whether misclassified smokers had been included. If they had not been, the results based on means should be ignored. In any case the results based on medians are to be preferred bearing in mind the skewness of the cotinine data.

It should not be forgotten that FONT did not show an RR increase in relation to spouse smoking that was significant at the 95% confidence interval and even when using a 90% confidence interval it was only marginally significant (lower limit 1.01). This implies that whatever estimates of lung cancer deaths attributable to ETS are calculated, they must have a limit of around zero. Nowhere is this made clear. Estimates from FONT are used to compare with estimates derived from 11 US studies to try to get some insight into how much the conclusions depend on the data assumed. Since FONT

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is one of the US studies, and a major one at that, the two sets of estimates are not independent. It might have been better to compare and contrast estimates based on FONT with those based on the other ten US studies.

3.2. Failure to characterize uncertainties properly

A strong message to the EPA from the SAB following review of EPA1 was to characterize better the uncertainties of the risk estimation procedure. In the conclusions in section 1 of the report it is stated that "an estimated range of 2,500 to 3,300 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States. The confidence in this range is medium to high with approximately 3,000 annual lung cancer deaths representing the best estimate". I submit that the range of 2,500 to 3,300 lung cancer deaths per year among nonsmokers totally fails to give any idea whatsoever of the true amount of uncertainty about the range.

The values of 2,500 (actually 2,480) and 3,300 come from Table 6-5 which represent point estimates from FONT based on two alternative Z-values, of 2.6 (using median cotinine levels) and 2.0 (using means). However this totally ignores sampling variation which on its own would make the lower limit close to zero whether one used data from FONT or from the combined US studies, since both have lower 90% confidence limits close to 1.00. If 95% confidence limits were used, which I have already argued is more appropriate, the lower limit would reach zero. When one additionally takes into

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account variation in the assumed value of numerous parameters in the estimation process, such as misclassification rates, frequency of smokers and exposure to ETS, and Z-values, and also takes into account the possibility that various biasing factors, ignored by EPA, actually are important, it is abundantly clear that the estimated range is hugely underestimated. Variability in the epidemiologic data does not exclude the possibility, for example, that the number of deaths among never smokers attributable to ETS might not be 2,000 but might be 12 as estimated by Arundel et al (see p 6-8 of EPA2) or even zero.

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PROBABLY WILL NOT USE THIS

3.22 Some minor points

Annex D lists some small errors I noted on detailed reading of chapters 5 and 6 of EPA2.

4. Hazard Identification I: Lung Cancer in Active Smokers, Long-term Animal Bioassays, and Genotoxicity Studies

Because of the dose-related relationship between lung cancer and tobacco smoking, EPA2, on page 4-1, concludes that it is "reasonable to theorize that exposure to environmental tobacco smoke (ETS) might also increase the risk of lung cancer in both smokers and nonsmokers". Later, on page 4-9, they state that the results "clearly establish the plausibility that ETS is also a human lung carcinogen" and affirm that "ETS exposure is a public health concern". Were this the overall thrust of the chapter, I would not disagree - the results cited do suggest a need to evaluate the possibility that ETS might cause lung cancer. It is when EPA2 switches tack and concludes that ETS can be classified, in the absence of epidemiological data on ETS, as a group A carcinogen that one must take issue.

In the first place it is not made clear that all the relevant components of the argument put forward in chapter 4 (the strong and dose-related epidemiology of active smoking, the fact that ETS contains many animal carcinogens present in mainstream smoke, and that nonsmokers are exposed to these carcinogens) could have been made many years ago, but that the scientific world at large did not

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start to express any need for action until after Hirayama and Trichopoulos published their early epidemiological results on ETS. Indeed, if the argument in chapter 4 is correct, one must inevitably wonder what a regulatory body such as EPA were doing sitting on these results for so long, when they could have classified ETS as a group A carcinogen 20 years ago.

The truth of course is that though the data cited in this chapter provide data to support the idea that an association is plausible, they do not of themselves prove that ETS causes lung cancer. There are a number of reasons for this:

(i) There may be chemical similarities between ETS and mainstream smoke but they are not the same. In the absence of any data demonstrating which chemicals or combinations of chemicals lead to the association of active smoking with lung cancer, one cannot be certain that relevant exposure occurs.

(ii) The fact that a threshold has not been observed for active smokers does not mean that one might not occur, even if ETS and mainstream smoke are essentially similar. There are obviously difficulties in choosing an appropriate smoke constituent for extrapolation. However it is certainly relevant to note that traditionally lung cancer in active smokers has been assumed to arise because of deposition of particulate matter in the lung, and that the amount of particulate matter retained in the lung is very much less from

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ETS than from mainstream smoke (a factor of about 2000 seems to be correct). Exposure from ETS might be below the threshold.

(iii) The data for active smoking have anyway not been properly examined to see whether a threshold does occur. The lowest groups in the prospective studies in Table 4-3 are in all cases broad, often include 10-a-day smokers, and always include 5-a-day smokers. No analyses have been conducted for 1-a-day or 2-a-day smokers to test whether any increase in risk is evident. (N.B. Such analyses should take care to consider the possibility that heavy smokers might misrepresent the amount they smoke.)

Other criticisms of the material presented in section 4 are as follows:

(i) In section 4.2.1. time trends in overall cigarette consumption are compared with time trends in overall lung cancer mortality rates. This is invalid because of the strong association of duration of smoking with lung cancer mortality. Overall lung cancer rates may be increasing at a time when there are clear declines in rates at younger ages, and it is absolutely necessary that trends be compared on a cohort basis for any meaningful conclusion to be drawn.

(ii) In section 4.2.3. it is stated that the "gradient for adenocarcinomas . . . is shallower than the slopes for other types [of lung cancer]". This understates the dramatic difference, and the very weak association of active smoking

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with adenocarcinoma. This is important as it should, but does not, lead in to the point that the relationship reported between ETS and adenocarcinoma in some studies is similar in magnitude to that reported between active smoking and lung cancer, which is difficult to interpret (inter alia because active smokers surely get much more ETS exposure than exposed nonsmokers).

(iii) The section, 4.3.1., on inhalation studies is inadequate. For balance it must be mentioned that rat and mouse inhalation studies have either produced no lung cancers or have produced at best equivocal results.

5. Some other points

On page 1-7 it is stated that "for the time period for which ETS exposure was of interest, spousal smoking is considered to be a better surrogate for ETS exposure in these [Japanese and Greek] societies than in Western countries, where other sources of ETS exposure . . . are generally higher". This is unsupported speculation and could well be untrue. In Japan, for example, many men spend little time at home and many women work.

On page 3-6 it is incorrectly stated that nicotine is specific to tobacco. Not so; it has been detected in tomatoes, aubergines, peppers and other solanaceous vegetables, and in tea, conceivably in large enough quantities to interfere somewhat with quantification of ETS exposure.

I MAY ADD TO THESE ON FURTHER READING — PROBABLY NOT: STOP HERE

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